

# RECENT DES RESEARCH

## Overview

This section of CDC's DES Update contains brief summaries of recently published research regarding the health of women and men who were exposed to DES. Each summary includes highlights from the study and a citation so you can look up the journal article if you want more information. Reading the entire article may give you a better understanding of the study. For help interpreting or understanding research results, refer to the section of CDC's DES Update titled [WHAT WE KNOW ABOUT DES: Understanding DES Research](#).

Although many DES studies have been published since 1971, only the most recent are summarized in this section. Following are the titles of the DES research summaries in this section.

- Cancer Risk in Women Exposed to Diethylstilbestrol In Utero
- Continued Follow-Up of Pregnancy Outcomes in DES-Exposed Offspring
- Cancer Risk in Men Exposed In Utero to Diethylstilbestrol
- Long-term Cancer Risk in Women Given Diethylstilbestrol During Pregnancy
- Infertility Among Women Exposed Prenatally to Diethylstilbestrol
- Incidence of Squamous Neoplasia of the Cervix and Vagina in Women Exposed Prenatally to Diethylstilbestrol (United States)
- Findings in Female Offspring of Women Exposed In Utero to Diethylstilbestrol
- Hypospadias in Sons of Women Exposed to Diethylstilbestrol In Utero: A Cohort Study
- Risk of Breast Cancer in Women Exposed to Diethylstilbestrol In Utero: Preliminary Results (United States)

The research summarized in this section can be considered trustworthy and was selected because

- each study had data from a substantial number of persons whose DES exposure was confirmed;
- the study was published in a journal that uses the peer-review process; and
- the researchers were considered objective and highly qualified to conduct the research.

As you read these research summaries, remember that researchers work with groups and averages. Situations exist in which a person's health does not fit the average experience represented in the research.



# RECENT DES RESEARCH

## Cancer Risk in Women Exposed to Diethylstilbestrol In Utero (Hatch et al., 1998)

In this study, the researchers wanted to learn whether women exposed to DES before birth (in the womb), known as DES Daughters, were more likely to develop cancer than unexposed women. Cancer rates of DES Daughters were also compared with cancer rates among women in the general population whose DES exposure status was unknown. At the time of this study, researchers accepted that DES exposure before birth increased a woman's risk of developing clear cell adenocarcinoma (CCA) of the vagina and cervix. However, researchers were not certain whether the risk for other types of cancer also increased.

Over a 16-year period, the researchers compared the medical histories of 3,650 DES Daughters with those of 1,202 unexposed women. The researchers then compared cancer rates from the two study groups to cancer rates for women in the general population whose DES exposure status was not known.

The researchers found that for DES Daughters, the rate for all types of cancer (other than CCA) was similar to the rates for unexposed women and women in the general population. In addition, DES Daughters were 40 times more likely than women in the general population to develop CCA.

Although this study was one of the largest of its kind, the study had some limitations. For example, the average age of DES Daughters who participated was 24 at the start of the study and 38 at last follow-up. The researchers suggested continued study of these DES Daughters for any increased cancer risks during menopausal years.

Another limitation of this study concerned breast cancer. Many studies have demonstrated that women exposed to estrogen in high doses or over a long period of time have an increased risk for breast cancer. However, breast cancer is most likely to occur in older women. Thus, the women in this study will have to be monitored over the next several decades to determine whether DES Daughters develop breast cancer at higher rates than do unexposed women.

Citation: Hatch EE, Palmer JR, Titus-Ernstoff L, Noller KL, Kaufman RH, et al. Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 1998;280:630-4.

# RECENT DES RESEARCH

## Continued Follow-Up of Pregnancy Outcomes in Diethylstilbestrol-Exposed Offspring (Kaufman et al., 2000)

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Health care providers and researchers who work with pregnant women have known for years that women exposed to DES before birth (in the womb), known as DES Daughters, often have difficulty conceiving and carrying a pregnancy to full term. Although the reasons for increased pregnancy complications among DES Daughters are not fully understood, the researchers of this study hypothesized that structural abnormalities in the cervix may account for increased miscarriages. The researchers compared the pregnancy histories of 3,373 DES Daughters with those of 1,036 unexposed women; these women comprised the largest study of pregnancy among DES Daughters to date.

The researchers found that DES Daughters had more negative outcomes during first pregnancies than unexposed women. Of DES Daughters, 64% delivered a full-term baby during their first pregnancy compared with 85% of unexposed women. Approximately 20% of DES Daughters experienced a miscarriage compared with 10% of unexposed women. Ectopic (tubal) pregnancy occurred in 4%–7% of DES Daughters, but less than 1% of unexposed women experienced this problem.

When considering all pregnancies, DES Daughters suffered more reproductive complications than unexposed women. Approximately 84% of DES Daughters had delivered at least one live birth compared with 87% of unexposed women. Approximately 30% of DES Daughters experienced a miscarriage compared with 24% of unexposed women. Of DES Daughters, 7%–11% had ectopic pregnancies, whereas only 1.9% of unexposed women had such a pregnancy. Premature births and miscarriages during the second trimester of pregnancy were also more common among DES Daughters than among unexposed women. Approximately 25% of DES Daughters had never been pregnant compared with approximately 19% of unexposed women.

Although many DES Daughters are now beyond their childbearing years, many younger DES Daughters still plan to have children. DES Daughters and their health care providers should be aware that these women are at an increased risk for a range of pregnancy complications. Extensive prenatal care may be needed for a pregnant woman exposed to DES or a woman trying to become pregnant who knows she was exposed to DES.

Citation: Kaufman RH, Adam E, Hatch EE, Noller KL, Herbst AL, et al. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. *Obstet Gynecol* 2000;96:483-9.

# RECENT DES RESEARCH

## Cancer Risk in Men Exposed In Utero to Diethylstilbestrol (Strohsnitter et al., 2001)

Since the discovery of an increased cancer risk among DES Daughters in 1971, some researchers have investigated whether men exposed to DES before birth (in the womb), known as DES Sons, also have an increased risk of cancer. Researchers hypothesized that DES exposure could increase the risk for testicular cancer because prenatal exposure to abnormal levels of other types of estrogen have been associated with this cancer. Previous studies of the relationship between exposure to DES before birth and an increased risk of testicular cancer were inconclusive. Some studies showed an increased rate of testicular cancer for DES Sons compared with unexposed men, and other studies indicated no differences.

The authors of this study conducted a follow-up study comparing the cancer rates of DES Sons with the cancer rates of unexposed men. A total of 2,759 men participated in the study, including 1,365 DES-exposed men and 1,394 unexposed men. The study included a review of death certificates for 48 men who died during 1978–1994 from any type of cancer. Researchers also reviewed the men's medical histories for 1978–1994, including any cancer risk factors (such as smoking or a previous history of cancer). The researchers compared the number of cancer cases in the DES-exposed men with the number of cancer cases in unexposed men. These rates also were compared with cancer rates for men in the general population (whose DES exposure status was not known).

The researchers found that the overall rate of cancer in DES Sons was not higher than the rate of cancer in the general population. However, the researchers did find that slightly more cases of testicular cancer occurred in DES-exposed men than in unexposed men, or than would be expected in the general population. Seven DES Sons were diagnosed with testicular cancer at ages 23–41, compared with two unexposed men ages 28 and 40.

Even with the higher rates of testicular cancer among DES Sons, the study did not prove an association between exposure to DES before birth and testicular cancer. The number of DES Sons diagnosed with testicular cancer was not large enough to prove an association. In other words, the higher rate of testicular cancer among DES Sons could have resulted from chance rather than exposure to DES. In addition, researchers did not know the amount of DES taken by mothers of the DES Sons in the study, or the timing of DES prescriptions during pregnancy. Dosage and timing could result in different cancer risks.

Citation: Strohsnitter WC, Noller KL, Hoover RN, Robboy SJ, Palmer JR, et al. Cancer risk in men exposed in utero to diethylstilbestrol. *Journal of the Natl Cancer Inst* 2001;93:545-51.

# RECENT DES RESEARCH

## Long-Term Cancer Risk in Women Given Diethylstilbestrol (DES) During Pregnancy (Titus-Ernstoff et al., 2001)

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Since the late 1970s, research has assessed the health risks for women prescribed DES while pregnant. Several studies conducted in the 1970s and 1980s demonstrated a modestly increased risk for breast cancer among DES-exposed women. However, not all findings were statistically significant, meaning that the higher rate of breast cancer among DES-exposed women could have resulted from chance rather than DES exposure. Other studies suggested that higher risks of endometrial (uterine) and ovarian cancer occurred in women prescribed DES while pregnant. Researchers were concerned about DES exposure and the increased risk for all three types of cancer because cancer of the breast, uterus, and cervix are all affected by exposure to hormones.

The researchers designed this study as a follow-up to evaluate long-term cancer risks, especially breast cancer, for women prescribed DES while pregnant. The medical records of women who participated in other research on DES exposure during pregnancy were studied. Information was gathered from 2,019 women prescribed DES while pregnant and 1,978 women who were not prescribed DES while pregnant. In addition, researchers studied the medical records of women from earlier studies who had died and determined how many of those deaths were the result of cancer. Using both sets of medical records, researchers were able to examine the medical records of 3,844 DES-exposed women and 3,716 unexposed women. With this information, the researchers compared the cancer rates of DES-exposed women to the cancer rates of unexposed women; they also compared the rates of cancer for these women in the study to the rates of cancer in the general population of women whose DES exposure status was not known.

The researchers found that women prescribed DES while pregnant had a 20%–30% higher risk of developing breast cancer than unexposed women and women in the general population. The researchers found no increased risk for any other cancers, including endometrial or ovarian cancer.

The findings of this study indicated that approximately 16% of women who were prescribed DES while pregnant developed breast cancer. In comparison, approximately 13% of women who were not prescribed DES while pregnant developed breast cancer. In other words, one in six women exposed to DES while pregnant are likely to develop breast cancer, compared with one in eight women not exposed to DES while pregnant. The increased risk of breast cancer did not appear to be interactive with other risk factors (such as use of hormone replacement therapy (HRT), use of birth control pills, or family history of breast cancer). That means that DES exposure, in addition to HRT or family history, did not increase the risk of breast cancer higher than that caused by DES exposure alone.

Citation: Titus-Ernstoff L, Hatch EE, Hoover RN, Palmer JR, Greenberg ER, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001;84:125-33.

# RECENT DES RESEARCH

## Infertility Among Women Exposed Prenatally to Diethylstilbestrol (Palmer et al., 2001)

For several decades, researchers have tried to determine whether exposure to DES before birth (in the womb) affects a woman's ability to become pregnant. Two earlier studies provided conflicting results that may have occurred because the women were in their early childbearing years when the studies were conducted and because their fertility histories were incomplete. In this study, the average age was 42; so these women had had many more reproductive years than women included in the two earlier studies.

This study compared the reproductive history of 1,753 DES Daughters with the reproductive history of 1,050 women not exposed to DES. The researchers found that compared with unexposed women, a greater number of DES Daughters had never become pregnant. Similarly, a greater number of DES Daughters, compared with unexposed women, tried for a year or more to become pregnant without success. In addition, researchers found that the timing of DES exposure in the womb (the trimester(s) during which exposure to DES took place) had some effect on infertility rates.

Specifically, 24% of DES Daughters had never become pregnant compared with 18% of unexposed women. Most DES Daughters who never became pregnant had been exposed to DES during the first 9 weeks in the womb. This finding supports earlier research, which found that structural abnormalities that affect fertility (such as endometriosis, abnormalities of the fallopian tubes, and inadequate production of cervical mucus) were more common among women whose DES exposure occurred during their mothers' first trimester of pregnancy.

Despite problems with becoming pregnant, 76% of DES Daughters eventually became pregnant compared with 82% of unexposed women.

Citation: Palmer JR, Hatch EE, Rao RS, Kaufman RH, Herbst AL, et al. Infertility among women exposed prenatally to diethylstilbestrol. *Am J Epidemiol* 2001;154:316-21.

# RECENT DES RESEARCH

## **Incidence of Squamous Neoplasia of the Cervix and Vagina in Women Exposed Prenatally to Diethylstilbestrol [United States] (Hatch et al., 2001)**

Women exposed to DES before birth (in the womb), known as DES Daughters, are at increased risk for clear cell adenocarcinoma (CCA) of the vagina and cervix, but the effect of in-utero DES exposure on later development of squamous neoplasia in the cervix and vagina is uncertain. This combined follow-up study of 3,899 DES Daughters (median age 38) and 1,374 unexposed daughters (median age 39) was followed 1982–1995. Subjects were drawn from three previously studied cohorts (DESAD, Dieckmann, and Horne). The purpose was to examine the long-term risk of developing high-grade squamous intraepithelial neoplasia (HSIL) of the genital tract in DES Daughters compared with unexposed daughters.

The study found a small but significant increase in HSIL among DES Daughters in all age groups, including those over age 40. A total of 111 pathology-confirmed HSIL cases occurred, including five of the vagina, one of the vulva and two cases of invasive cervical cancer. The overall relative risk was 2.1 among DES-exposed versus unexposed. The relative risk among those whose mothers were prescribed DES within 7 weeks of the last menstrual period was 2.8 compared with 1.35 among women exposed for the first time at 15 weeks or later. Women with documented high-grade neoplasia before 1982 were excluded because prior treatment of the cervix may lower the subsequent finding of intraepithelial neoplasia. Researchers could not rule out that more frequent and intensive screening among DES-exposed women played a role in these findings.

Neoplasia is abnormal and uncontrolled cell growth; a neoplasm is new growth of benign or malignant tissue. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts. These flat cells look like fish scales under a microscope. Squamous intraepithelial lesion (SIL) is a general term for the abnormal growth of squamous cells on the surface of the cervix. The changes in the cells are described as low grade or high grade, depending on how much of the cervix is affected and how abnormal the cells appear. Cervical intraepithelial neoplasia (CIN) is a general term for the growth of abnormal cells on the surface of the cervix. Numbers from 1 to 3 may be used to describe how much of the cervix contains abnormal cells. High-grade squamous intraepithelial lesion (HSIL) is a precancerous condition in which the cells of the uterine cervix are moderately or severely abnormal. In this study, grades 2 and 3 were considered high. (Adapted from National Cancer Institute Dictionary, available at URL: <http://cancer.gov/dictionary/>.)

Citation: Hatch EE, Herbst AL, Hoover RN, Noller KL, Adam E, Kaufman RH, et al. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol [United States]. *Cancer Causes Control* 2001;12:837–45.

# RECENT DES RESEARCH

## Findings in Female Offspring of Women Exposed In Utero to Diethylstilbestrol (Kaufman et al., 2002)

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Although previous laboratory animal studies found cancer of the uterus and cervix in female offspring of DES Daughters, thus far, few studies have focused on health problems in third-generation humans (the offspring of DES Daughters and Sons). This article is a preliminary report from an ongoing study of third-generation DES health effects.

The researchers recruited DES Daughters who participated in the National Collaborative Diethylstilbestrol Adenosis (DESAD) cohort study. Twenty-six DES Daughters agreed to participate with their daughters. Each of the 28 third-generation daughters filled out a questionnaire and had a gynecological examination, during which the pelvis, abdomen, breasts, and cervix were inspected, a colposcopy of the cervix and vagina was performed, a cervical-vaginal smear was obtained from the upper vagina and the cervix, and an iodine staining of the vagina and cervix was performed. The results of this examination were compared with the same type of examination performed on their mothers (DES Daughters) during the earlier DESAD study.

In the previous DESAD study, researchers found that 16 of the 26 DES Daughters had cervical or vaginal changes. In the current study of third-generation daughters, no abnormalities of the lower genital tract were detected. However, the researchers cautioned that the sample size of 26 DES Daughters and 28 third-generation daughters was too small to detect an increased risk of genital tract abnormalities.

A second limitation of this study was the age of the participants. A mean age for the third-generation daughters of 20.1 years (age range: 15–28 years) may have been too young to detect clear cell adenocarcinoma (CCA) of the vagina and cervix, which is more often found in older unexposed women. A third limitation of this study was the possibility that results were biased by the self-selection of participants. Only 26 of 70 eligible DES Daughters and 28 of their third-generation daughters participated in this study. These women may not be representative of all eligible participants. However, most women who did not participate declined because they were unavailable or had been told by a gynecologist that they did not have abnormalities.

Citation: Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2002;99:197-200.

# RECENT DES RESEARCH

## **Hypospadias in Sons of Women Exposed to Diethylstilbestrol In Utero: A Cohort Study (Klip et al., 2002)**

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Although laboratory animal studies have reported third-generation (offspring of DES Daughters and Sons) health effects of DES exposure, little is known about human health effects in the children of the women exposed to DES before birth. The goal of this study was to examine the risk of hypospadias (abnormality of the penis) in the sons of women exposed to DES before birth.

This Dutch cohort study consisted of a questionnaire of 16,284 women with diagnosed fertility problems. The researchers compared the prevalence of the rate of hypospadias between the sons of mothers who had been exposed to DES before birth with sons whose mothers had not been exposed to DES. The mothers of 205 sons reported DES exposure, and four of these sons had confirmed hypospadias; eight sons of the remaining 8,729 sons in the study had hypospadias. Risk of hypospadias was not affected by maternal age, fertility treatment, or use of assisted reproductive techniques.

Results suggested that although absolute risk was small, the third-generation health effects of DES exposure warrant additional studies.

Citation: Klip H, Verloop J, van Gool JD, Koster META, Burger CW, van Leeuwen FE. Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 2002; 359:1102-7.

# RECENT DES RESEARCH

## **Risk of Breast Cancer in Women Exposed to Diethylstilbestrol In Utero: Preliminary Results (United States). (Palmer et al., 2002)**

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In this prospective follow-up study, researchers wanted to learn whether women exposed to DES before birth (in the womb), known as DES Daughters, were more likely to develop breast cancer than unexposed women. Information on reproductive factors, behavioral risk factors and health problems, including breast cancer, was gathered in 1994 from 4,821 DES Daughters and 2,095 unexposed women. Three years later, 3,916 DES Daughters and 1,746 unexposed women completed a short follow-up questionnaire that asked about new occurrences of disease. The researchers confirmed results of the surveys by checking medical reports or death certificates. The data revealed that 43 cases of breast cancer occurred among DES Daughters and 15 cases occurred among the unexposed.

Findings of the study are not definitive, but suggest that exposure to DES before birth (in the womb) may be associated with an increased risk of breast cancer. The risk of breast cancer for DES Daughters as a whole group is slightly higher than estimated in earlier studies (Hatch, 1998), but is not a statistically significant increase (that means the higher incidence of breast cancer could be the result of chance, rather than being associated with exposure to DES).

The study findings were different, depending upon the age of the study participants.

DES Daughters under age 40 did not have a higher risk of breast cancer than unexposed women under 40. However, DES Daughters who were over 40 years old who participated in the study were 2½ times more likely to experience breast cancer than were unexposed women over age 40. The increased risk was statistically significant (not due to chance, but increased risk was more likely to be related to association with DES exposure).

It is important to note that the findings from this study are viewed as preliminary due to some limitations of the research. Although participants had been followed for an average of 19 years, the median age of the study group in 1997 was 43 years, an age when breast cancer incidence is still relatively low in the general population. Continued investigation as the group of DES Daughters grow older is necessary to have enough data to determine if DES exposure is indeed linked to an increased risk of breast cancer among women exposed before birth (in the womb).

In addition, while the DES Daughters and unexposed women in the study were similar in most respects, they differed in some important areas. DES Daughters in the study were more likely to be older when they gave birth to their first child or to have had fewer or no children than were unexposed women. Both these characteristics have been associated with increased incidence of breast cancer and raise questions about whether DES exposure or other characteristics might be responsible for increased risks.

Citation: Palmer JR, Hatch EE, Rosenberg CL, Hartge P, Kaufman RH, Titus-Ernstoff L, et al. Risk of breast cancer in women exposed to diethylstilbestrol in utero: preliminary results (United States). *Cancer Causes Control* 2002;13:753-8.